Acta Pharmaceutica Turcica XXXVIII (1) 1-4, 1996

ANALYSIS OF MOISTURE CONTENT IN HARD GELATIN CAPSULES AT DIFFERENT STABILITY CONDITIONS

SERT JELATİN KAPSÜLLERİN DEĞİŞİK STABİLİTE ORTAMLARINDAKİ NEM İÇERİKLERİNİN ANALIZI

K. CANEFE, A. BOZKIR and S. BADRİ

Faculty of Pharmacy, University of Ankara, Department of Pharmaceutical Technology, Tandoğan, Ankara, Turkey.

The moisture adsorption properties of the capsule dosage forms which were produced in our laboratory have been investigated in this study at different temperature and moisture conditions. For this purpose three active substances (caffeine, procaine hydrochloride and ammonium chloride), showing distinct physical reactions to temperature and humidity, have been selected and moisture adsorption was observed on empty capsules. We also analyzed by the equations of adsorption and the data well fitted the B.E.T. equation for empty capsules. However the use of adsorption equations for filled capsules indicated that no significant results were obtained for their moisture adsorption features.

Bu çalışmada, laboratuar ortamında hazırlanan kapsül formundaki ilaçların farklı sıcaklık ve nem içeren ortamlardaki nem adsorbsiyonu özellikleri incelenmiştir. Bu amaçla nem ve sıcaklığa karşı değişik fiziksel özellik gösteren 3 etken madde (kafein, prokain hidroklorür ve amonyum klorür) seçilmiştir. Boş kapsüllerde nem adsorbsiyonu belirlenmiş ve bu adsorbsiyonun B.E.T. eşitligine uyduğu saptanmıştır. Buna karşılık dolu kapsüllerin nem adsorbsiyonu incelenmesinde anlamlı bir sonuca ulaşmak mümkün olmamıştır.

Keywords : *Gelatin capsule; Relative humidity; Moisture transfer; Isotherm*

Anahtar kelimeler : *Jelatin kapsül; Relatif nem; Nem transferi; İzoterm*

Introduction

The interaction of water with pharmaceutical solids occurs virtually in all stages of manufacture, from synthesis of raw materials to storage of the final dosage form. The amount of water associated with a solid at a particular relative humidity and temperature depends on a number of available sites of interaction. As environmental conditions change, the empty gelatin capsules have a tendency to gain or lose moisture.

Generally, as relative humidity (RH) is increased (at constant temperature) or temperature decreased (at constant relative humidity) moisture uptake (sorption) will occur. Conversely, decreasing relative humidity (at constant temperature) or increasing temperature (at constant relative humidity) will lead to a moisture loss (desorption). Such changes in environmental conditions can occur during storage, filling and packaging potentially altering the properties of the capsules. Another factor that warrants serious consideration is the transfer of moisture between gelatin capsules and the contents of the capsules (1-4).

Several studies have appeared in the pharmaceutical literature demonstrating the transfer of water from gelatin capsules to their contents. Strickland and Moss (1962) reported moisture transfer to pentobarbital sodium (5). Bond et al. (1970) described similar phenomena for cephalexin and Bell et al. (1973) for sodium cromoglycate (6-7). Ito et al. (1969) demonstrated that water-insoluble excipients with high sorptive capacities (i.e. Avicel and corn starch) are also involved in moisture transfer between materials in this dosage form (8). Grimm and Schepky (1980) have demonstrated how, depending on the sorption isotherms of the capsule fill, a capsule shell can lose moisture to the capsule fill and become brittle or, conversely, under opposite sorption isotherm conditions can draw moisture out of the fill and become soft (9). York (1981) has reported on the moisture isotherms of gelatins. Knowing the moisture isotherm of the powder mixture in the gelatin, it is possible to calculate the shift in moisture from shell to powder mixture (10). Zografi et al. (1988) have developed and tested a mathematical method to predict the final relative water vapor pressure in a closed system for a multicomponent mixture of solids knowing the initial water content for each component (11). Kontny et al. (1989) used this method for unresolved questions concerning gelatine capsule britleness under constant temperature conditions and indicated that the sorption- desorption moisture transfer (SDMT) model predicts a priori the final relative humidity in a closed system of several materials of varying moisture contents (12).

In this study, three active substances showing distinct physical reactions against temperature and humidity have been selected and filled in capsules. Their stabilities have been followed for a period of twelve months, then moisture content of empty and filled hard gelatin capsules were analyzed by the equations of adsorption.

Materials

Caffeine (BDN), procaine hydrochloride (Merck), ammonium chloride (Merck).

All the other materials and reagents were of pharmaceutical and analytical reagent grade.

Methods

1. Optimized storage conditions

1.1. In the refrigerator[1]; 4±1°C and 30± 6%, 50±5%, 70 2%, 90 2% RH

1.2 In the climatic chamber[2]; 22±1°C and 30±6%, 50±5%, 70±2%, 90±2% RH

1.3 In the oven[3]; 37±1°C and 30±6%, 50±5%, 70±2%, 90±2% RH (13).

2. Capsule filling and storage process

The equilibrium of empty capsules was maintained under appropriate conditions in a desiccator containing silicagel. Active substances were filled[4] into the capsules (number one) and stored at relative humidity equilibrium during a period of 12 months.

3. The quality controls of hard gelatin capsules

The quality controls of these capsules have been made at a (t=0) time as the begining of the stability tests. The same quality controls have been tested at the periods of 1, 3, 6, 9, 12 months. The main quality controls were: Organoleptic, weight deviation, disintegration time, dissolution rate, active ingredient quantity.

Adsorbed moisture content was determined in empty and filled capsules and evaluated. Physico-pharmaceutical controls have been investigated at a previous work (14).

4.Determination of adsorbed moisture content

4.1. Empty capsules: These were initially dried at a temperature of 25°C under vacuum conditions using desiccators, containing appropriate saturated salt solutions, until constant weight was attained.

4.2. Filled capsules : Capsule weight and moisture content were determined initially and during a period of twelve months for filled capsules.

All water vapor uptake isotherms were generated gravimetrically.

Results and Discussion

Physical properties of hard gelatin capsules are important factors for drug stabilities. For this purpose the amount of adsorbed moisture content of hard gelatin capsules at different temperatures were calculated and are shown in Table 1.

Table 1. The amount of adsorbed moisture content of empty gelatin capsules at different temperatures.

P/Po (*)	4 1°C	22 1°C	37 1°C
	x/m(**)	x/m	x/m
30±6	9.48	7.51	5.81
50±5	11.97	9.90	7.78
70±2	15.24	12.82	10.41
90±2	26.99	22.26	23.17

(*) Relative moisture (%)

(**) Adsorbed water mol. number per one gram gelatine capsule (x/m: $mol.g^{-1}.10^{-3}$)

1 Arçelik-Arbec 365 A

2 Nüve ID 300, Elimko 4000

3 Heraus-FT 420; Heraus-B 5050

4 Capsule filling machine : Brevetti Zuma-Milan

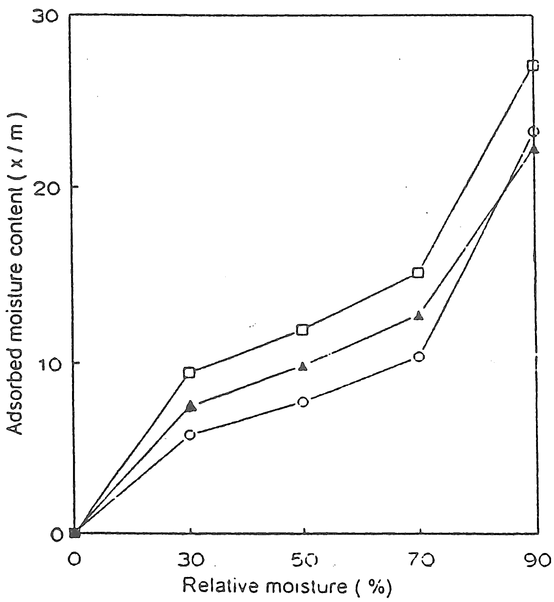

Fig. 1. Adsorbed moisture contents of empty capsules by the B.E.T. equation at temperatures 4±1°C (□), 22±1°C (△) and 37±1°C (o)

The equations of adsorbtion were analyzed and the data for empty gelatin capsules' moisture content well fitted the B.E.T. equation (Fig.1).

The moisture content, at the end of the 12th month, of the hard gelatin capsules filled with the active ingredients are shown in Table 2.

The maximum moisture adsorbtion in empty capsules was obtained at 4±1°C (Table 1). When the temperature was increased a decrease of moisture content was observed according to the principal of Le Chatelier (7, 12).

We also observed the higher value of adsorbed moisture content at 22°C and 37°C. Even at 37°C and 90% RH the moisture content value was higher than at 22°C. In this case we decided that there is an increasement in diffusion in capsules at higher temperatures so it causes an increase in the moisture content by diffusion through the capsules shell at 37°C. According to empty capsules moisture content kinetical evaluation the data well fitted B.E.T. equation at 4, 22 and 37°C as reported previously (7, 12, 15-17).

Table 2. The data of experimental moisture content in hard gelatin capsules containing caffeine, procaine hydrochloride and ammonium chloride at different conditions.

Temperature (°C)	P/Po (%)	Caffeine x/m(*)	Procaine HCl x/m (*)	Ammonium chloride x/m (*)
4±1	30±6 50±5 70±2 90±2	-3.48 -1.29 0.67 7.07	-1.32 -0.95 1.10 9.99	-0.75 -0.58 1.46 22.90
22±1	30±6 50±5 70±2 90±2	-3.16 2.24 6.07 29.20	-2.66 0.38 3.57 25.90	-0.98 0.92 7.52 10.90
37±1	30±6 50±5 70±2 90±2	-4.67 -1.59 -7.51 12.40	-5.86 -4.53 -2.98 5.08	-3.71 -7.07 -4.41 1.49

(*) x/m: $mol.g^{-1}.10^{-4}$

In filled hard gelatin capsules, moisture content was analyzed for different active ingredients having various physical properties. We chose caffeine as flowered substance, ammonium chloride as light hygroscopic substance and procaine hydrochloride as an inert substance. Capsule moisture contents versus time at different conditions were analyzed. The maximum adsorbed moisture content was observed at 22°C for capsules containing caffeine and procaine hydrochloride. The maximum moisture adsorbtion value was found at 4°C for capsules containing ammonium chloride The highest moisture desorbtion values were found for all the active ingredients at 37°C. This result fitted the rule of Le Chatelier for capsules containing ammonium chloride. But the data proved us that the adsorbtion and desorbtion results are very complex for different active ingredients. The desorbtion and adsorbtion content depend on initial moisture content, production condition and physical properties of the active ingredients. For these reasons detailed analyses should be done about moisture content of hard gelatin capsules with active ingredient.

References

1. Canefe, K., Bozkır, A.: 9 th Pharmaceutical Technology Conference Vol. 1, p. 324-353, 1990
2. Canefe, K., Bozkır, A.: Pharmacia 30 (3) 126 (1990)
3. Carstensen, J.T.: Drug Stability, Principles and Practices, Marcel Dekker Inc., Newyork 1990
4. Grimm, W., Thomae, K.: Stability Testing of Drug Products, Verlagsgesellschaft, Stuttgart 1987
5. Strickland, W.A., Moss, M. : J.Pharm.Sci. 51, 1002 (1962)
6. Bond, C.M., Lees, K.A., Packington, J.L.: Pharm. J. 210 (1970)
7. Bell, J.H., Stevenson, N.A., Taylor, J.E.: J.Pharm. Pharmacol. 25th Supp. 96 (1973)
8. Ito, K., Kaga, S., Takeya, Y.: Chem. Pharm. Bull. 17, 1134 (1969)
9. Grimm, W., Schepky, G.: Stabilitats Prufung in der Pharmazie, Editio Cantor, Aulendorf, Fed. Rep. Germany 216-230, 1980
10. York, P.: J.Pharm. Pharmacol. 33, 269 (1981)
11. Zografi, G., Grandolfi, G.P., Kontny, M.J. et al.: Int. J.Pharm. 42, 77 (1988)
12. Kontny, M.J., Mulski, C.A.: Int. J.Pharm. 54, 79 (1989)
13. Pharmaceutical Handbook, 19th Ed. The Pharmaceutical Press, London 1980
14. Badri, S.: An Investigation on the Physical Pharmaceutical Stabilities of Drugs in Capsule Forms.-M.S. Thesis, University of Ankara, Faculty of Pharmacy, Ankara 1993
15. Melia, C.D., Hadgraft, J., Kellaway, I.W. et al.: Int. J. Pharm. Tech. and Prod. Mfr. 6 (4) 13 (1985)
16. Brunauer, S., Deming, L.S., Deming, W.E. et al.: J.A. Chem. Soc. 62, 1723 (1940)
17. Brunauer, S.: Physical Adsorption of Gases and Vapors, Oxford Univ. Press, London 1943

Accepted : 04.04.1995